PROTOCOL

Official Title: Deep brain stimulation effects on gait and balance in patients with Parkinson's disease

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1. STUDY DESIGN AND SCHEMA:

Gait and balance problems are dopamine resistant features of Parkinson's disease (PD). Deep brain stimulation of sub-thalamic nucleus (STN–DBS) is an established surgical method that improves motor symptoms and gait in PD, however it may produce unexpected freezing of gait and balance problems in some patients, presumably due to overstimulation and gait incoordination. The aim of this study is to identify the differential effects of unilateral STN stimulation versus bilateral stimulation on gait kinematics in patients with PD and associated gait dysfunction.

2. BACKGROUND AND RATIONALE :

Freezing of gait (FOG) and walking difficulties represent perhaps the most difficult challenges in the treatment of Parkinson's disease (PD). PD patients experience frequent difficulty initiating walking, shuffling and postural instability (Vu, Nutt et al. 2012). In spite of dopaminergic therapy, walking difficulties continue to progress and only rarely do non-dopaminergic treatments provide benefit. Deep brain stimulation of sub-thalamic nucleus (STN-DBS) improves motor scores, walking and FOG (St George, Nutt et al. 2010). In some patients, even after appropriate fine tuning of programming, walking and balance continue to be a problem. One explanation can be the progression of the disease, however in some cases the FOG appears soon after the DBS. This has been attributed to overstimulation and perhaps asymmetric stimulation in the networks involved in gait

control. Several studies have looked at the parameters of stimulation and have concluded that reducing the frequency of stimulation would ameliorate walking difficulties (Fasano, Herzog et al. 2011). Similarly, reducing the amplitude contralateral to the most affected side is associated with less FOG (Moreau, Defebvre et al. 2008).

A growing body of literature suggests that right-hemisphere circuitry seems to be more affected than the left in patients with FOG (Fling, Cohen et al. 2013) and that patients with worse symptoms on the left are more likely to develop postural instability gait dysfunction (PIGD) (Giladi, McDermott et al. 2001)

3. OBJECTIVES

In this study we aim to evaluate the effects of differential STN stimulation on walking. We hypothesize that in patients with FOG, unilateral stimulation on the most affected hemisphere will ameliorate walking in a higher degree than bilateral stimulation. Functional asymmetry of STN was shown before by other studies (Castrioto, Meaney et al. 2011) and is thought that unilateral STN stimulation has effects that are similar with bilateral STN on UPDRS motor scores, effect called dominant STN. Since the effects of unilateral stimulation on walking are not completely understood, we plan to determine if unilateral stimulation has differential effects on gait kinematics.

4. STUDY POPULATION

Inclusion criteria are: patients with idiopathic PD with Hoehn and Yahr Stage 1-3 that have undergone STN-DBS and had developed difficulty walking 6-12 months after the DBS on stable dosage dopamine agonist/levodopa, expected to remain on the same dosage of treatment for the next 3 months; age 45-70.

Exclusion criteria are: past medical history of seizures, renal insufficiency and history of cardiac arrhythmia, previous DBS, severe arthritis, women of childbearing potential, dementia and less than 45 and over 70 years old.

5. MEASUREMENTS AND EVALUATION

This study is meant to see if there is improvement in gait or freezing of gait after changes in the stimulation parameters.

- In the first part of the study subjects (1 visit) will be randomly assigned to four different stimulation parameters: both stimulators ON, both stimulators off, right stimulator ON, left stimulator ON. We will assess participants' gait using clinical scales as well as wearable sensors attached to the body. Assessments will be done one hour after each change in the stimulation parameters.
- In the second part of the study that participants may be asked to participate in, changes in the frequency of stimulation and contact stimulation will be performed. Four different stimulation settings will be tested. In this part evaluations will be done.

PART 1

Screening: At this visit, the study investigator will discuss the details of the research study and the consent form with the study participant.

The following procedures will also be completed:

- Sign informed consent form.
- Collection of a complete medical history and a neurological exam.
- United Parkinson's disease rating scale (UPDRS) will be performed by a Movement Disorder Specialist to assess the severity of Parkinson's disease.

- Timed Up and Go test (TUG) - a mobility test that is used to measure the basic mobility skills of people who are elderly or have neurological conditions such as PD and it includes a sit-to-stand component as well as walking 3m, turning and returning to the chair.
- Freezing of Gait Questionnaire (FOGQ) which is a self-report questionnaire consisting of 16 items regarding falls and walking problems.
- Gait analysis using wearable sensors (Mobility Lab) to measure the walking speed and step length.

If study subjects meet the eligibility criteria, they will be asked to sign the informed consent and asked to come to clinic for part 1 or for part 2 of the study without taking their Parkinson's medication for 12 hours.

Visit 1 Changes to the DBS stimulator will be done every 60 minutes for 4 hours in a random order.

- Bilateral stimulators ON, bilateral stimulators OFF, Right ON-Left OFF, Right OFF-Left ON.
- UPDRS scale
- Gait analysis using wearable sensors (Mobility Lab) to measure the walking speed and step length.

This visit will take about 5 hours. At the end of the visit study participants will go home with their initial settings.

PART 2

Screening: At this visit, the study investigator will discuss the details of the research study. The following procedures will be completed:

- United Parkinson's disease rating scale (UPDRS) will be performed by a Movement Disorder Specialist to assess the severity of their Parkinson's disease.

- Timed Up and Go test (TUG) - a mobility test that is used to measure the basic mobility skills of people who are elderly or have neurological conditions such as PD that includes a sit-to-stand component as well as walking 3m, turning and returning to the chair.
- Freezing of Gait Questionnaire (FOGQ) which is a self-report questionnaire consisting of 16 items regarding falls and walking problems.
- Gait analysis using wearable sensors (Mobility Lab) to measure the walking speed and step length.
- The PI will review the medical records to assess if precise localization of the electrode contacts can be done using the CT scan that was performed post-operatively and will decide if an MRI of the brain is necessary to perform.

Visits 1, 2, 3 and 4

During these visits the stimulation settings will be changed to one of the following conditions: Low frequency stimulation-dorsal STN, Low frequency stimulation- ventral STN, High frequency stimulation- dorsal STN, High frequency stimulation –ventral STN

After each change the following tests will be performed:

- United Parkinson's disease rating scale (UPDRS) will be performed by a Movement Disorder Specialist to assess the severity of Parkinson's disease.
- Timed Up and go test (TUG) - a mobility test that is used to measure the basic mobility skills of people who are elderly or have neurological conditions such as PD and it includes a sit-to-stand component as well as walking 3m, turning and returning to the chair.
- Freezing of Gait Questionnaire (FOGQ) which is a self-report questionnaire consisting of 16 items regarding falls and walking problems.
- Gait analysis using wearable sensors (Mobility Lab) to measure the walking speed and step length.
- Clinical Global Improvement Scale

6. ASSESSMENT AND REPORTING OF ADVERSE EVENTS

Patients will be monitored in the office for three hours to assess for any side effects, which may include worsening tremors, voice changing or worsening rigidity.

Serious Adverse Events (SAE)*: Adverse Events will be monitored and logged and reported to the IRB.*

7. STATISTICAL ANALYSIS

For the data analysis, we will estimate frequencies of adverse events, central tendency and variability for patient's demographic characteristics, velocity, stride length, TUG and the UPDRS score. All analyses will be conducted using SAS (version 9.2, SAS Institute Inc., Cary, NC).

8. ADHERENCE TO ETHICAL, REGULATORY AND ADMINISTRATIVE CONSIDERATIONS

Written IRB approval will be obtained from the University of Miami Institutional Review Board (IRB) and from each IRB with jurisdiction over the participating Nodes as well as the individual CTPs when indicated. Approval will be obtained for all aspects of the study, including the assessment of the risk/benefit ratio, informed consent process and document, procedures and rating instruments, randomization, clinical services, and videotaping. Informed consent will also be obtained from the therapists to permit analyses of data by therapist characteristics and therapy process. Any changes that impact the risk/benefit ratio of the study as well as changes to the protocol or to the consent process will be submitted and approved by each IRB prior to implementation. No advertising or direct soliciting of participants will be initiated without IRB approval of all written flyers/brochures/ documents.

9. REFERENCES

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